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Reproductive factors and epithelial ovarian cancer survival in the EPIC cohort study

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Background: Reproductive factors influence the risk of developing epithelial ovarian cancer (EOC), but little is known about their association with survival. We tested whether prediagnostic reproductive factors influenced EOC-specific survival among 1025 invasive EOC cases identified in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, which included 521 330 total participants (approximately 370 000 women) aged 25–70 years at recruitment from 1992 to 2000.

Methods: Information on reproductive characteristics was collected at recruitment. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), and multivariable models were adjusted for age and year of diagnosis, body mass index, tumour stage, smoking status and stratified by study centre.

Results: After a mean follow-up of 3.6 years (± 3.2 s.d.) following EOC diagnosis, 511 (49.9%) of the 1025 women died from EOC. We observed a suggestive survival advantage in menopausal hormone therapy (MHT) users (ever *vs* never use, HR = 0.80, 95% CI = 0.62–1.03) and a significant survival benefit in long-term MHT users (⩾5 years use *vs* never use, HR = 0.70, 95% CI = 0.50–0.99, $P_{trend} = 0.04$). We observed similar results for MHT use when restricting to serous cases. Other reproductive factors, including parity, breastfeeding, oral contraceptive use and age at menarche or menopause, were not associated with EOC-specific mortality risk.

Conclusions: Further studies are warranted to investigate the possible improvement in EOC survival in MHT users.

Ovarian cancer is the seventh most common cause of cancer mortality among women worldwide and the most lethal gynaecological malignancy (Allemani *et al*, 2014). It is well established that epithelial ovarian cancer (EOC) has a hormonal aetiology as evidenced by the lower risk of developing EOC among women who are parous (Riman *et al*, 2004; Whittemore *et al*, 1992) or oral contraceptive (OC) users (Beral *et al*, 2008; Tsilidis *et al*, 2011; Fortner *et al*, 2015) and the higher EOC risk with use of menopausal hormone therapy (MHT) (Beral *et al*, 2015). The changes in steroid hormone signalling that underlie these risk associations are complex and little understood; however, in general it is thought that higher oestrogen levels may promote ovarian carcinogenesis (Cramer and Welch, 1983; Cunat *et al*, 2004), while higher levels of progestins and progesterone may have a protective

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role against EOC (Risch, 1998; Modugno *et al*, 2012). Given the association between reproductive factors and EOC incidence, and its hypothesised hormonal aetiology, it is plausible that reproductive factors may also influence EOC prognosis.

Patient age and tumour characteristics, such as stage and histological subtype, are important prognostic factors. For example, cases diagnosed with the most common (serous) histological subtype of EOC have a poor prognosis as compared with other subtypes (endometrioid, mucinous and clear cell) (Rosen *et al*, 2009). Epidemiological studies may provide further insights about the possible links between reproductive factors and EOC survival while accounting for known clinical prognostic factors. In a large Australian case–control study including 676 EOC cases (419 deaths) (Nagle *et al*, 2008), women who had ever *vs* never breastfed had an improved survival, but there was no trend with breastfeeding duration. In contrast, other studies (Jacobsen *et al*, 1993; Kjaerbye-Thygesen *et al*, 2006; Robbins *et al*, 2009; Zhang and Holman, 2012) reported no association with breastfeeding. In a prospective study of 644 EOC cases (419 deaths) from a Norwegian breast screening cohort (Jacobsen *et al*, 1993), an older age at first birth was associated with worse survival but there was no apparent trend, and this result was not confirmed by other studies (Kjaerbye-Thygesen *et al*, 2006; Nagle *et al*, 2008; Yang *et al*, 2008). Three previous studies (each with $\geqslant 649$ EOC cases identified from population-based case–control studies) investigated MHT use and observed no influence on survival among all EOC cases (Mascarenhas *et al*, 2006; Nagle *et al*, 2008; Wernli *et al*, 2008); however, in the two studies that evaluated serous cases, one reported improved survival in ever *vs* never users of MHT (HR = 0.69, 95% CI 0.48–0.98) (Mascarenhas *et al*, 2006), while there was no association in the other study (Nagle *et al*, 2008). Because of the inconsistent findings reported across studies, further research is needed to assess the possible influence of reproductive factors on EOC survival. In the current study, we investigated prediagnostic reproductive characteristics in relation to EOC-specific survival among EOC cases overall and serous cases in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

MATERIAL AND METHODS

Study population. The study design has been previously detailed (Riboli *et al*, 2002). In brief, the EPIC cohort includes >500 000 individuals, of which approximately 370 000 are women. The participants were mainly recruited from the general population who resided in 23 study centres in 10 European countries, Denmark, France, Spain, Germany, The Netherlands, Greece, Italy, Norway, Sweden and the United Kingdom, between 1992 and 2000. Exceptions to this included: French participants were recruited through health insurance databases; some members of the Italian and Spanish cohorts were recruited via local blood donor registries; some members of the Utrecht and Florence cohorts were recruited through local breast screening programmes; and approximately half of the Oxford cohort included individuals who did not eat meat. Ethics approval for the study was obtained from the International Agency for Research on Cancer and the local review boards at the participating centres.

Outcome assessment. According to the improved understanding of ovarian cancer pathogenesis (Jarboe *et al*, 2008; Kurman and Shih, 2011), we defined incident 'ovarian' cancer cases using the International Classification of Disease for Oncology (ICD-O-3) codes C56.9, C57.0 and C48, including primary peritoneal and fallopian tube cancers. Cases were identified through linkage with national cancer registries in Denmark, Italy, The Netherlands, Norway, Spain, Sweden and the UK. In France, Germany and Greece, cases were identified using insurance records, cancer registries and active follow-up of participants. Data on tumour invasiveness, histology, stage and grade were available from cancer registries and a pathology record review. Information on vital status, the causes and dates of death were obtained using record linkages with cancer registries, boards of health and death indices in Denmark, Italy (except Naples), The Netherlands, Norway, Spain, Sweden and the UK or through active follow-up (inquiries by mail or telephone to participants, municipal registries, regional health departments, physicians and hospitals) in Germany, Greece, Naples (Italy) and France. Causes of death were reported as specified by the International Statistical Classification of Diseases, Tenth revision (ICD-10). As different procedures were used to obtain follow-up data on vital status across the study centres, this resulted in differences across the centres in the timing to report the causes of death. To account for this, the follow-up dates were truncated to when 80% of the causes of death at each centre were known (June 2005–June 2009) with the following exceptions; in Greece and Germany, the date of last known contact was the date of censoring and this extended to November 2009 for Greece and February 2010 for Germany. Data were unavailable to examine recurrent EOC in the current study.

We identified 1405 ovarian cancer cases and the following exclusions were used: not first incident ($n = 60$); non-epithelial cancer or unknown histology ($n = 95$); missing date of death ($n = 4$); unknown vital status ($n = 2$); ovarian cancer diagnosed after the vital status censoring date ($n = 84$); date of diagnosis was the same as date of death ($n = 6$); missing extensive information on reproductive history, specifically age at menarche, number and age at first full term pregnancy (FTP), OC use and breastfeeding duration ($n = 28$); borderline EOC cases ($n = 99$); tumours missing invasiveness ($n = 2$); leaving 1025 invasive EOCs in the current analysis. The outcome of interest was death from EOC or an EOC-related cause, defined as death owing to possible metastatic tumours, including peritoneum not otherwise specified (NOS), specified parts of the peritoneum, fallopian tube, corpus uteri and uterus NOS. Of the $n = 554$ total deaths that were observed, an EOC-specific death was recorded for $n = 511$ (92%) and deaths that occurred owing to other causes ($n = 43$) were censored.

Exposure assessment. At the time of study recruitment, participants completed questionnaires on reproductive history, diet and lifestyle. Data collection procedures were centralised as a single study with multiple centres. Reproductive variables that were investigated included parity (live births and still births only; number and age at first FTP), ever breastfed and duration, OC use and duration, age at menarche and menopause, hysterectomy and total ovulatory lifespan. For the MHT variables (assessed at recruitment), participants were asked if they had ever used MHT, the timing of use (whether they were current users), their age at start and total duration of use. The duration of MHT use refers to the total duration for the former users or the duration up until the time of recruitment among the current users. Information on MHT formulation was only available from women who reported that they were currently using MHT at recruitment. Information on the time since last MHT use was unavailable. Menopausal status was defined using information on menstruation status, hysterectomy, oophorectomy, use of exogenous hormones and age as detailed previously (Lahmann *et al*, 2004). Breastfeeding duration was only available for the first three and the last FTP, therefore for women reporting >4 FTPs the duration was estimated as the number of pregnancies multiplied by the mean duration of breastfeeding per child. The total ovulatory lifespan was calculated as the difference between a participant's age at menopause and their age at menarche (postmenopausal) or the difference between their age at recruitment and age at menarche (premenopausal, perimenopausal), less the time that she was pregnant, calculated as the number of FTPs multiplied by

0.75 (equivalent to 9 months), and/or used OCs. Data on tubal ligation, family history of ovarian cancer and BRCA1/2 status were not available for any of the cases. Age at last FTP was not assessed because this information was unknown for 88% of the parous cases and family history of breast cancer was not examined as a confounder because this information was missing for 56% of the cases.

Statistical analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models. Person-time was calculated as the number of days between EOC diagnosis and the date of death, emigration, loss to follow-up or censoring, whichever occurred first. Multivariable models were adjusted for covariates that were selected *a priori* because of their known influence on risk of EOC death; age at diagnosis (continuous), BMI ($<23\,kg\,m^{-2}$, $\geqslant23-<25$ (reference), $\geqslant25-<30$, $\geqslant30$), tumour stage (local (reference), regional, metastatic, unknown) and smoking status (never (reference), former, current, unknown). We further adjusted for the year of diagnosis (continuous) to account for possible changes in the treatment regime for ovarian cancer over time. All models were stratified by study centre. We tested whether additional adjustment for the following potential confounders (education level, marital status, physical activity and alcohol intake) or tumour characteristics (histologic subtype and grade) changed the risk estimates by $\geqslant10\%$ (Greenland, 1989), but the risk estimates were very similar therefore none of these factors were included in the final models. Other than education level, additional measures of social class were not available in this study. The P_{trend} was calculated by entering continuous terms into the regression model. Analyses were conducted using the survival package (Therneau, 2014) in R version 3.0.2 (R Core Team, 2014). The proportional hazards assumption was tested using the method described by Grambsch and Therneau, 1994.

We carried out the following stratified analyses by: age at diagnosis (<65 years, $\geqslant65$ years), because older women may be less likely to be offered standard treatments and more likely to develop toxicity (Tew *et al*, 2014); BMI ($<25\,kg\,m^{-2}$, $\geqslant25\,kg\,m^{-2}$) because obese women may have a decreased survival owing to surgical complications and/or inadequate chemotherapy dosing (Modesitt and van Nagell, 2005); histological subtype (serous, non-serous, including endometrioid, mucinous and clear cell); and tumour stage (early-stage/FIGO SI/II, late-stage/FIGO SIII (Prat, 2014)). Interaction terms (P_{int}) between the binary stratifying variables and the categorical reproductive variables were included in multivariable models and were compared with models without interaction terms using the likelihood ratio test. Sensitivity analyses were carried out after restricting analyses to a uniform subgroup of cases that were classified as the most common (serous) histological subtype, cases who were diagnosed with SII/III tumours, cases with tumours from the ovary (C56.9) only and participants who were postmenopausal at recruitment. We also examined MHT use variables after additionally adjusting for hysterectomy status. Statistical significance was set at $P<0.05$.

RESULTS

The study population included 1025 women diagnosed with EOC. The median (range) of the participant ages was 54 years (26, 86) and 61 years (34, 98) at the baseline questionnaire completion and at cancer diagnosis, respectively. During a mean follow-up of 3.6 years (±3.2 s.d.), 511 individuals (49.9%) died from ovarian cancer. Survival analysis of clinical and demographic characteristics showed that older age, poorly/undifferentiated tumour grade, advanced stage and current smoking at the study baseline were associated with a worse EOC-specific survival (Table 1). Compared with serous cases, women with endometrioid tumours had a better prognosis (HR = 0.53, 95% CI = 0.37–0.75), whereas cases with NOS tumours had a poorer prognosis (HR = 1.41, 95% CI 1.11–1.79).

We investigated reproductive factors that were assessed on average 5.9 years (±3.4 s.d.) prior to the diagnosis of EOC. In the

Table 1. Association between clinicopathological and demographic factors in relation to survival among EOC cases

	Total[a] *n*	Fatal cases[b] *n*(%)	HR[c]	95% CI
Age at diagnosis[d], years				
<50	103	44 (42.7)	Ref.	
50–59	361	160 (44.3)	1.25	0.88–1.79
60–69	411	218 (53.0)	1.68	1.17–2.41
70+	150	89 (59.3)	2.58	1.71–3.90
P_{trend}				<0.001
Tumour site				
Ovary	960	482 (50.2)	Ref.	
Other[e]	65	29 (44.6)	1.01	0.67–1.53
Histology				
Serous	568	298 (52.5)	Ref.	
Mucinous	74	27 (36.5)	1.16	0.77–1.77
Endometrioid	126	39 (31.0)	0.53	0.37–0.75
Clear cell	49	13 (26.5)	0.82	0.46–1.46
NOS	164	111(67.7)	1.41	1.11–1.79
Other[f]	44	23 (52.3)	1.20	0.77–1.90
Grade[g]				
Well differentiated	64	13 (20.3)	Ref.	
Moderately differentiated	210	95 (45.2)	1.99	1.07–3.70
Poorly/undifferentiated	345	193 (55.9)	2.41	1.31–4.43
FIGO stage[h]				
Stage I	141	21 (14.9)	Ref.	
Stage II	78	27 (34.6)	2.77	1.54–4.98
Stage III	300	176 (58.7)	6.34	3.96–10.17
Stage IV	101	61 (60.4)	10.54	6.16–18.03
Stage[i]				
Local	138	18 (13.0)	Ref.	
Regional	171	62 (36.3)	3.31	1.94–5.64
Metastatic	586	360 (61.4)	8.64	5.32–14.04
Body mass index, kg m^{-2}				
<23	318	149 (46.9)	0.99	0.76–1.28
23–24.9	235	114 (48.5)	Ref.	
25–29.9	316	169 (53.5)	1.01	(0.79–1.30)
30+	156	79 (50.6)	0.85	(0.62–1.16)
Smoking status[j]				
Never smoker	567	285 (50.3)	Ref.	
Former smoker	235	113 (48.1)	1.09	(0.86–1.37)
Current smoker	204	104 (51.0)	1.56	(1.22–1.99)

Abbreviations: CI = confidence interval; EOC = epithelial ovarian cancer; FIGO = International Federation of Gynecology and Obstetrics; HR = hazard ratio; NOS = not otherwise specified.

[a]Total number of cases $n = 1025$.

[b]Total number of fatal cases $n = 511$.

[c]Adjusted for age at diagnosis (continuous), year of diagnosis (continuous), BMI ($<23\,kg\,m^{-2}$, $\geqslant23-<25$ (reference), $\geqslant25-<30$, $\geqslant30$), tumour stage (local (reference), regional, metastatic and unknown), smoking status (never (reference), former, current and unknown) and stratified by study centre.

[d]Adjusted for all factors mentioned above in footnote c except for age at diagnosis as this was the variable of interest.

[e]Includes fallopian tube and primary peritoneal carcinomas.

[f]The 'other' histological subtype category included 'Neoplasm, malignant' (31.8%), 'Carcinoma, undifferentiated, NOS' (25.0%) and 'Carcinosarcoma, NOS' (11.4%) and a small number of 'Carcinoma, anaplastic, NOS', 'Pseudosarcomatous carcinoma, NOS', 'Transitional cell carcinoma, NOS', 'Solid carcinoma, NOS', 'Mullerian mixed tumour', 'Mesodermal mixed tumour' and 'Brenner tumour, malignant'.

[g]Grade was missing for 39.6% of the cohort.

[h]FIGO stage was missing for 39.5% of the cohort.

[i]Stage is closely related to FIGO stage but is more complete across the cohort (12.7% missing).

[j]Smoking status was missing for 1.9% of the cohort.

Table 2. Association between prediagnostic reproductive factors and survival among EOC cases overall						
	Total[a] *n*	Fatal cases[b] *n* (%)	Model 1 HR[c]	95% CI	Model 2 HR[d]	95% CI
Age at menarche[e], years						
<12	158	83 (52.5)	Ref.		Ref.	
12	187	86 (46.0)	0.89	0.65–1.22	1.01	0.74–1.38
13	253	125 (49.4)	0.91	0.68–1.22	0.84	0.63–1.13
14	223	107 (48.0)	0.84	0.62–1.13	0.75	0.55–1.01
>14	186	100 (53.8)	0.93	0.68–1.27	0.90	0.66–1.24
P_{trend}				0.76		0.37
Parous[e]						
No	169	86 (50.9)	Ref.		Ref.	
Yes	833	414 (49.7)	0.97	0.77–1.24	0.90	0.71–1.14
Number of FTPs[e,f]						
1	159	75 (47.2)	Ref.		Ref.	
2	394	190 (48.2)	1.07	0.81–1.41	1.04	0.78–1.38
3+	262	142 (54.2)	1.17	0.88–1.57	1.10	0.81–1.49
P_{trend}				0.13		0.31
Age at first FTP[e,f], years						
⩽20	118	66 (55.9)	Ref.		Ref.	
>20–⩽25	376	167 (44.4)	0.65	0.48–0.87	0.66	0.49–0.90
>25–⩽30	244	125 (51.2)	0.72	0.53–0.99	0.72	0.52–1.00
>30	88	52 (59.1)	0.87	0.59–1.26	0.86	0.58–1.28
P_{trend}				0.70		0.59
Breastfeeding[f,g]						
Never	120	59 (49.2)	Ref.		Ref.	
Ever	660	327 (49.5)	0.82	0.61–1.11	0.83	0.61–1.12
Duration of breastfeeding[e,h], months						
⩽3	205	104 (50.7)	Ref.		Ref.	
>3–⩽6	122	58 (47.5)	0.88	0.62–1.23	1.02	0.71–1.45
>6–⩽12	156	75 (48.1)	0.76	0.55–1.04	0.88	0.63–1.22
>12–⩽24	127	61 (48.0)	0.84	0.60–1.19	0.97	0.68–1.39
>24	47	28 (59.6)	1.10	0.69–1.73	1.11	0.69–1.79
P_{trend}				0.90		0.87
OC use[e]						
Never	523	273 (52.2)	Ref.		Ref.	
Ever	495	232 (46.9)	1.04	0.86–1.26	0.96	0.79–1.17
Duration of OC use[i,j], years						
⩽1	112	45 (40.2)	Ref.		Ref.	
>1–⩽5	164	71 (43.3)	0.88	0.59–1.32	0.98	0.65–1.48
>5–⩽10	101	47 (46.5)	1.12	0.72–1.74	1.26	0.80–1.98
>10	77	49 (63.6)	1.69	1.08–2.64	1.74	1.10–2.75
P_{trend}				0.006		0.01
Age at menopause[k,l], years						
⩽45	89	52 (58.4)	0.94	0.66–1.33	1.06	0.74–1.53
>45–⩽50	207	121(58.5)	Ref.		Ref.	
>50–⩽52	94	50 (53.2)	0.90	0.64–1.27	0.98	0.69–1.40
>52	136	77 (56.6)	0.90	0.66–1.22	1.04	0.76–1.41
P_{trend}				0.91		0.71
MHT use[e,k,m]						
Never	299	176 (58.9)	Ref.		Ref.	
Ever	233	130 (55.8)	0.85	0.66–1.09	0.80	0.62–1.03
MHT timing of use at baseline[e,k,m]						
Former	69	41 (59.4)	0.94	0.66–1.33	0.85	0.59–1.22
Current	160	88 (55.0)	0.84	0.63–1.12	0.79	0.59–1.06
MHT duration of use at baseline[k,m,n], years						
<5	121	68 (56.2)	0.99	0.73–1.34	0.95	0.69–1.29
⩾5	86	49 (57.0)	0.76	0.54–1.07	0.70	0.50–0.99
P_{trend}				0.11		0.04
MHT formulation at baseline (current users only)[k,m,o]						
E only	37	24 (64.9)	0.84	0.54–1.31	0.86	0.54–1.35
E+P	100	52 (52.0)	0.89	0.62–1.27	0.80	0.55–1.16
Other	12	8 (66.7)	1.08	0.50–2.33	0.92	0.42–2.01
Hysterectomy[p]						
No	831	411 (49.5)	Ref.		Ref.	
Yes	88	45 (51.1)	0.75	0.54–1.04	0.79	0.57–1.10

Table 2. (Continued)

	Total[a] n	Fatal cases[b] n (%)	Model 1 HR[c]	95% CI	Model 2 HR[d]	95% CI
Total ovulatory years[q]						
⩽27.5	212	105 (49.5)	Ref.		Ref.	
>27.5–⩽33.0	207	99 (47.8)	0.87	0.65–1.17	0.91	0.67–1.23
>33.0–⩽36.5	212	94 (44.3)	0.72	0.53–0.96	0.72	0.53–0.97
>36.5	194	106 (54.6)	0.87	0.65–1.17	0.97	0.71–1.31
P_{trend}				0.04		0.12

Abbreviations: CI = confidence interval; EOC = epithelial ovarian cancer; FTP = full term pregnancy; HR = hazard ratio; MHT = menopausal hormone therapy; OC = oral contraceptive.
[a]Total number of cases $n = 1025$.
[b]Total number of fatal cases $n = 511$.
[c]Adjusted for age at diagnosis (continuous) and stratified by study centre.
[d]Adjusted for age at diagnosis (continuous), year of diagnosis (continuous), BMI (<23 kg m^{-2}, ⩾23–<25 (reference), ⩾25 –<30, ⩾30), tumour stage (local (reference), regional, metastatic and unknown), smoking status (never (reference), former, current and unknown) and stratified by study centre.
[e]Missing for <5% of the cohort.
[f]Among parous women only.
[g]Breastfeeding was missing for 6.4% of the cohort.
[h]Among parous women who had ever breastfed.
[i]Among OC users only.
[j]Duration of OC use was missing for 8.3% of women.
[k]Among postmenopausal women only.
[l]Age at menopause was missing for 18.6% of postmenopausal women.
[m]Participants from Greece and Sweden were excluded from this analysis as detailed data on MHT use were unavailable.
[n]MHT duration was missing for 11.2% of individuals who ever used MHT.
[o]MHT formulation was missing for 6.9% of individuals who reported current use.
[p]Hysterectomy was missing for 10.3% of the cohort.
[q]Total ovulatory years was missing for 19.5% of the cohort.

analyses of EOC overall, ever *vs* never OC use was not associated with EOC-specific survival (HR = 0.96, 95% CI = 0.79–1.17) but among OC users a longer duration of use was associated with a worse survival (>10 years *vs* ⩽1 year of use: HR = 1.74 95% CI = 1.10–2.75, $P_{trend} = 0.01$; Table 2). Compared with never users of MHT, long-term users (⩾5 years *vs* never users; HR = 0.70, 95% CI = 0.50–0.99, $P_{trend} = 0.04$) had a better prognosis, and there was a non-significant improved survival among ever users (HR = 0.80, 95% CI = 0.62–1.03). There was no apparent influence on survival according to the timing of MHT use (former or current use at the study baseline) or when MHT formulation was evaluated among current users at baseline. In the sensitivity analyses of MHT variables when including additional adjustment for hysterectomy status, we observed similar results to those reported above (data not shown). In the analyses of age at first FTP, we observed a better survival among women who had their first FTP at age >20–⩽25 years as compared with age ⩽20 (HR = 0.66, 95% CI = 0.49–0.90), but there was no association with the other age at first FTP categories and no apparent trend ($P_{trend} = 0.59$). Finally, there was no association between other reproductive characteristics (parity, number of FTPs, ever breastfed or duration, age at menarche or menopause, hysterectomy or total ovulatory years) and EOC-specific survival. There were no apparent differences in any of the risk associations when stratifying by age at diagnosis or BMI ($P_{int} \geqslant 0.07$) (data not shown). When restricting analyses to cases diagnosed with an ovarian primary tumour (not primary peritoneal or fallopian tube site), we observed similar results to those reported above (data not shown).

In the analyses restricted to serous cases, there was little influence of OC use or duration, or other reproductive factors such as parity or breastfeeding, on EOC-specific survival (Table 3). Similar to analyses of EOC overall, we observed better survival among serous cases who reported an age at first FTP of >20–⩽25 years *vs* age ⩽20 (HR = 0.59, 95% CI = 0.38–0.92), but none of the other age categories were associated with risk, and there was no evidence of a trend ($P_{trend} = 0.75$). Compared with serous cases who never used MHT, we observed better survival among ever users of MHT (HR = 0.63, 95% CI = 0.44–0.90) and a stronger association with long-term use (⩾5 years MHT use *vs* never use, HR = 0.55, 95% CI = 0.35–0.87, $P_{trend} = 0.01$) and with current, but not former, use (current MHT use at baseline *vs* never use, HR = 0.60, 95% CI = 0.39–0.90). We carried out exploratory analyses to compare reproductive factors between serous and non-serous cases and observed significant heterogeneity in the risk associations for MHT use and OC duration of use ($P_{int} \leqslant 0.01$) (Supplementary Table 1). In contrast with the improved survival observed among serous cases who reported MHT use, there appeared to be a higher risk of death among non-serous cases who used MHT. Given that only 23 deaths occurred among 45 non-serous cases who reported MHT use, this finding should be interpreted with caution.

In a uniform subgroup of FIGO stage II/III cases (all histological subtypes), there was no association between OC use or OC duration of use with EOC-specific survival (Supplementary Table 2). Compared with never users of MHT, we observed a non-significant improved survival with ever use of MHT in stage II/III cases (HR = 0.67, 95% CI = 0.41–1.08), but there was no trend with duration of MHT use ($P_{trend} = 0.45$). Although based on only 29 stage II/III cases with an early menopause, we observed a worse survival in women who reported an early age at menopause (menopause age ⩽45 years *vs* ⩾45–⩽50, HR = 2.05, 95% CI = 1.04–4.01); this result contrasted with the null association with menopausal age that was observed in the analyses of EOC overall and serous cases. We carried out further stratified analyses to compare risk associations between cases diagnosed with early stage (FIGO SI/II) *vs* late stage (FIGO SIII) tumours and observed no significant heterogeneity ($P_{int} \geqslant 0.06$) (data not shown). In the sensitivity analyses restricted to postmenopausal cases at recruitment ($n = 646$) whose reproductive exposures were unlikely to change, we observed similar results to analyses of EOC overall (Supplementary Table 3). Finally, compared with never users of MHT (crude analyses), MHT users tended to be younger, had a slightly lower BMI, were more likely to ever use OCs and used OCs for a longer duration and a higher proportion were diagnosed with serous tumours (Supplementary Table 4). There were no differences for other factors, including tumour grade or stage in relation to MHT use.

Table 3. Association between prediagnostic reproductive factors and survival among serous EOC cases

	Total[a] *n*	Fatal cases[b] *n* (%)	Model 1 HR[c]	95% CI	Model 2 HR[d]	95% CI
Age at menarche[e], years						
<12	84	48 (57.1)	Ref.		Ref.	
12	102	50 (49.0)	0.98	0.64–1.51	1.10	0.71–1.69
13	145	76 (52.4)	0.92	0.62–1.38	0.82	0.55–1.23
14	134	67 (50.0)	0.86	0.58–1.30	0.79	0.52–1.20
>14	98	54 (55.1)	1.02	0.66–1.57	0.92	0.59–1.44
P_{trend}				0.80		0.69
Parous[e]						
No	86	49 (57.0)	Ref.		Ref.	
Yes	474	245 (51.7)	0.94	0.68–1.30	0.96	0.69–1.33
Number of FTPs[e,f]						
1	101	48 (47.5)	Ref.		Ref.	
2	215	109 (50.7)	1.22	0.85–1.76	0.95	0.64–1.39
3+	148	82 (55.4)	1.47	1.00–2.16	1.10	0.73–1.65
P_{trend}				0.05		0.38
Age at first FTP[e,f], years						
⩽20	61	31 (50.8)	Ref.		Ref.	
>20–⩽25	208	94 (45.2)	0.68	0.44–1.04	0.59	0.38–0.92
>25–⩽30	145	83 (57.2)	0.82	0.53–1.28	0.75	0.47–1.20
>30	56	35 (62.5)	0.76	0.45–1.28	0.71	0.40–1.23
P_{trend}				0.65		0.75
Breastfeeding[f,g]						
Never	69	34 (49.3)	Ref.		Ref.	
Ever	376	192 (51.1)	0.88	0.59–1.31	0.92	0.61–1.38
Duration of breastfeeding[h], years						
⩽3	130	65 (50.0)	Ref.		Ref.	
>3–⩽6	75	39 (52.0)	1.05	0.68–1.61	1.07	0.68–1.69
>6–⩽12	75	33 (44.0)	0.61	0.38–0.98	0.60	0.37–0.99
>12–⩽24	69	38 (55.1)	0.93	0.59–1.45	0.90	0.56–1.43
>24	27	17 (63.0)	1.12	0.62–2.02	1.13	0.61–2.08
P_{trend}				0.59		0.48
OC use[e]						
Never	275	148 (53.8)	Ref.		Ref.	
Ever	289	147 (50.9)	1.01	0.78–1.31	0.95	0.73–1.23
Duration of OC use[i,j], years						
⩽1	67	30 (44.8)	Ref.		Ref.	
>1–⩽5	94	50 (53.2)	0.96	0.58–1.60	1.05	0.61–1.78
>5–⩽10	58	26 (44.8)	0.92	0.52–1.64	1.15	0.63–2.12
>10	46	28 (60.9)	1.42	0.80–2.51	1.31	0.71–2.40
P_{trend}				0.31		0.42
Age at menopause[k,l]						
⩽45	52	33 (63.5)	1.26	0.79–2.02	1.38	0.83–2.30
>45–⩽50	112	65 (58.0)	Ref.		Ref.	
>50–⩽52	55	29 (52.7)	0.98	0.61–1.58	0.97	0.58–1.61
>52	68	45 (66.2)	1.16	0.77–1.77	1.11	0.71–1.75
P_{trend}				0.88		0.64
MHT use[e,k,m]						
Never	151	94 (62.3)	Ref.		Ref.	
Ever	144	80 (55.6)	0.71	0.50–1.00	0.63	0.44–0.90
MHT timing of use at baseline[e,k,m]						
Former	42	25 (59.5)	0.86	0.54–1.38	0.73	0.45–1.18
Current	101	54 (53.5)	0.65	0.44–0.96	0.60	0.39–0.90
MHT duration of use at baseline[k,m,n], years						
<5	78	43 (55.1)	0.81	0.54–1.22	0.79	0.51–1.21
⩾5	52	29 (55.8)	0.64	0.41–1.00	0.55	0.35–0.87
P_{trend}				0.07		0.01
MHT formulation at baseline (current users only)[k,m,o]						
E only	21	16 (76.2)	0.74	0.41–1.32	0.64	0.34–1.18
E+P	65	32 (49.2)	0.63	0.39–1.01	0.61	0.36–1.02
Other	7	3 (42.9)	0.35	0.08–1.53	0.35	0.08–1.50
Hysterectomy[p]						
No	452	231 (51.1)	Ref.		Ref.	
Yes	58	31 (53.4)	0.82	0.55–1.23	0.80	0.53–1.21

Table 3. (Continued)

	Total[a] *n*	Fatal cases[b] *n* (%)	Model 1 HR[c]	95% CI	Model 2 HR[d]	95% CI
Total ovulatory years[q]						
⩽27.5	119	57 (47.9)	Ref.		Ref.	
>27.5–⩽33.0	117	65 (55.6)	1.34	0.90–1.98	1.33	0.87–2.04
>33.0–⩽36.5	124	55 (47.4)	0.75	0.49–1.13	0.73	0.47–1.13
>36.5	101	61 (60.4)	1.22	0.80–1.84	1.22	0.79–1.88
P_{trend}				0.74		0.72

Abbreviations: CI = confidence interval; EOC = epithelial ovarian cancer; FTP = full term pregnancy; HR = hazard ratio, MHT = menopausal hormone therapy; OC = oral contraceptive.
[a]Total number of serous cases $n = 568$.
[b]Total number of fatal serous cases $n = 298$.
[c]Adjusted for age at diagnosis (continuous) and stratified by study centre.
[d]Adjusted for age at diagnosis (continuous), year of diagnosis (continuous), BMI (<23 kg m^{-2}, ⩾23–<25 (reference), ⩾25–<30, ⩾30), tumour stage (local (reference), regional, metastatic and unknown), smoking status (never (reference), former, current and unknown) and stratified by study centre.
[e]Missing for ⩽2.1% of the cohort.
[f]Among parous women only.
[g]Breastfeeding was missing for 6.1% of the cohort.
[h]Among parous women who had ever breastfed.
[i]Among OC users only.
[j]Duration of OC use was missing for 8.3% of women.
[k]Among postmenopausal women only.
[l]Age at menopause was missing for 18.5% of postmenopausal women.
[m]Participants from Greece and Sweden were excluded from this analysis as detailed data on MHT use were unavailable.
[n]MHT duration was missing for 9.7% of individuals who ever used MHT.
[o]MHT formulation was missing for 7.9% of individuals who reported current use.
[p]Hysterectomy was missing for 10.2% of the cohort.
[q]Total ovulatory years was missing for 18.8% of the cohort.

DISCUSSION

To our knowledge, the current study was the largest to date to investigate reproductive factors and EOC-specific survival. In the analyses of EOC overall, compared with never users of MHT, long-term MHT users had a better survival and there also was a non-significant improved survival in ever users of MHT. In contrast, previous studies of ever *vs* never use of MHT reported no influence on survival (Mascarenhas *et al*, 2006; Nagle *et al*, 2008; Wernli *et al*, 2008; Zhang and Holman, 2012). Similar to earlier studies (Mascarenhas *et al*, 2006; Wernli *et al*, 2008), we observed no difference in survival according to MHT formulation. Among serous cases, in comparison with never users of MHT, we observed a better survival among women who had ever used MHT and specifically among long-term and current MHT users at the study baseline. The observation of an improved survival among serous cases for ever *vs* never MHT use is consistent with an earlier Swedish study (Mascarenhas *et al*, 2006), while the only other study that investigated serous EOC (Nagle *et al*, 2008) reported no association. These results highlight the possibility that MHT use may have a divergent influence on EOC, wherein MHT users may have a better survival, which contrasts with the increased risk of developing incident serous (and endometrioid) EOC based on a recent meta-analysis of 52 epidemiological studies (Beral *et al*, 2015). Further studies are needed to investigate MHT use in relation to survival among serous cases and to extend this analysis to other individual histological subtypes of EOC as we were unable to address this issue in the current study owing to the limited sample size.

Consistent with earlier studies (Kjaerbye-Thygesen *et al*, 2006; Nagle *et al*, 2008; Yang *et al*, 2008; Robbins *et al*, 2009; Zhang and Holman, 2012), we observed that ever use of OCs was not associated with EOC survival; however, in the current study a longer duration of OC use among ever users of OCs was unexpectedly associated with a worse survival. This result contrasted with two prior reports that observed no influence of OC duration on EOC survival (Kjaerbye-Thygesen *et al*, 2006; Yang *et al*, 2008). In the current study, there was no association between OC duration and survival in the analyses restricted to serous cases. As this was the only report where a longer duration of OC use was associated with worse survival in EOC overall, this may be a chance finding.

We noted that the following reproductive factors, namely, parity, breastfeeding, age at menarche and menopause, hysterectomy and total ovulatory years were not associated with EOC-specific survival in the analyses of EOC overall or serous cases. These null associations were consistent with the earlier Australian study and systematic review of seven studies (Nagle *et al*, 2008) and subsequent reports (Yang *et al*, 2008; Zhang and Holman, 2012; Robbins *et al*, 2009), with the following exceptions: reproductive factors that were associated with a worse survival included an older age at first delivery (Jacobsen *et al*, 1993), younger age at menarche and increasing ovulatory years (Kjaerbye-Thygesen *et al*, 2006; Robbins *et al*, 2009), while breastfeeding was associated with a better survival (Nagle *et al*, 2008).

Key strengths of this study include the large number of cases and the representation of findings from 10 European countries. Potential limitations of this study were that the exposure data were collected on average 6 years prior to diagnosis; however, the impact of this was likely limited for reproductive exposures that occurred during childbearing years; the majority (63%) of the cases in the study were postmenopausal at recruitment and had completed their reproductive history. Furthermore, in sensitivity analyses that were restricted to postmenopausal women, we observed similar results to the overall analysis. For MHT, it would have been informative if follow-up questionnaire data were available to compare use before and after diagnosis; however, we only had information on MHT use at recruitment in the current study. Thus it is possible that some of the current MHT users may have ceased their use after recruitment, or non-MHT users at baseline might have subsequently commenced MHT use; these factors would be expected to attenuate the risk estimates towards the null. We used a summary staging variable (local, regional, metastatic and unknown) to adjust for the extent of disease, but data were unavailable for other prognostic factors such as the amount of

residual disease remaining after surgery and information on treatment. To account for possible variation in the treatment offered between the EPIC study centres, we stratified by the study centre in all the statistical models. As treatment is likely to be uniform following tumour staging guidelines (Prat, 2014), we adjusted for stage to account for potential differences in the treatment received. Finally, as a large number of statistical tests were performed in this analysis, the significant results may be chance findings.

In conclusion, in this report from the EPIC study we observed that most reproductive factors did not appear to influence survival from EOC. Together with results from the earlier Swedish study (Mascarenhas *et al*, 2006), our findings strengthen the evidence for a possible improvement in survival for serous EOC cases who had ever used MHT. It will be important to investigate this result further particularly in relation to the timing of MHT use and to examine whether MHT use may be associated with survival in individual non-serous histological subtypes of EOC.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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